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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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QUARLES & BRADY LLP
FIRSTAR PLAZA, ONE SOUTH PINCKNEY STREET
P.O. BOX 2113 SUITE 600
MADISON WI 53701-2113

EXAMINER	
HUTSON, R	
ART UNIT	**PAPER NUMBER**
1652	9

DATE MAILED: 01/02/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/234,028	Ronald T. Raines
Examiner	**Group Art Unit**
Richard Hutson	1652

☒ Responsive to communication(s) filed on *Oct 12, 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-14* is/are pending in the applicat

Of the above, claim(s) *11-14* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-10* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *2 & 6*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Election/Restriction

Claims 1-14 are still at issue and are present for examination.

Applicant's election with traverse of Group I, Claims 1-10 in Paper No. 8 is acknowledged. The traversal is on the ground(s) that coexamination of Groups I and II would not require independent searches. This is not found persuasive because while the searches for the groups overlap, they are not coextensive. The search for Groups I and II would each require the search of subclasses unnecessary for the search of elected Group II. For example, search of Group I would require search of subclass 530/350 and search of Group II would require search of subclass 536/23.5.

The requirement is still deemed proper and is therefore made FINAL.

Claims 11-14 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 8.

Specification

1. The disclosure is objected to because of the following informalities: On page 7, lines 30 and 31 the specification refers to "amino acids 94 and 95, at both amino acid positions 238 or

239,..." This is not in agreement with the amino acid positions in the claims and found elsewhere throughout the specification.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1, 3, 4, 5, 6, 7 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 (3, 4, 5, 6, 7 and 8 dependent from) is indefinite in that it is confusing in the recitation "a mutant ribonuclease inhibitor having at least one amino acid substitution in at least one of its adjacent cysteine residues to an amino acid residue not capable of forming a disulfide bond..." While it is believed that the applicants are attempting to claim a mutant ribonuclease inhibitor wherein said mutation is in at least one of two adjacent cysteine residues, to an amino acid residue not capable of forming a disulfide bond, this is unclear. The claim reciting "a mutant ribonuclease inhibitor having at least one amino acid substitution in at least one of its adjacent cysteine residues to an amino acid residue not capable of forming a disulfide bond..."

may also be interpreted as a mutant ribonuclease inhibitor wherein a cysteine residue adjacent to an amino acid residue not capable of forming a disulfide bond is mutated.

Claims 2 and 10 are further confusing in their recitation of "the substituted cysteine residue is in at least one of positions 94, 95, 328 and 329." Examination of the sequence of the human ribonuclease inhibitor shows that adjacent cysteine residues are found at positions 95, 96, 329 and 330. Thus this discrepancy is confusing.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

6. Claims 1-10 are directed to all possible mutant ribonuclease inhibitors having at least one amino acid substitution in at least one of its adjacent cysteine residues to an amino acid residue not capable of forming a disulfide bond, the mutant ribonuclease inhibitor having a greater resistance to oxidation, the mutant ribonuclease inhibitor retaining its specificity and binding affinity to ribonuclease (claim 1) or angiogenin (claim 9), wherein said substituted cysteine residue is in at least one of positions 94, 95, 328 and 329 (claims 2 and 10), wherein said cysteine residue is substituted with an alanine residue (claim 3), wherein said cysteine residue substitution

inhibits formation of a disulfide bond (claim 4), wherein said mutant is 10 to 15 fold more resistant to oxidative damage than the native human ribonuclease inhibitor (claim 5), wherein the ribonuclease is of the RNase A superfamily (claim 6), wherein said RI inhibits ribonucleolytic activity in vitro (claim 7), wherein said mutant ribonuclease inhibitor is derived from the native human ribonuclease inhibitor (claim 8). The specification, however, only provides the representative species in which the cysteines at amino acid positions 94, 95, 328 and 329 of human ribonuclease inhibitor are mutated to alanines, encompassed by these claims. There is no disclosure of any particular structure to function/activity relationship in the single disclosed species. The specification also fails to describe additional representative species of these mutant ribonuclease inhibitors by any identifying structural characteristics or properties other than the activities recited in claim 1 and the disclosed cysteine modifications, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

7. Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a mutant human ribonuclease inhibitor wherein said mutation is a substitution in at least one of its two adjacent cysteine residues to an amino acid residue not capable of forming a disulfide bond, the mutant ribonuclease inhibitor having a greater resistance to oxidation, the mutant ribonuclease inhibitor retaining its specificity and binding affinity to

ribonuclease, does not reasonably provide enablement for any mutant ribonuclease inhibitors having at least one amino acid substitution in at least one of its adjacent cysteine residues to an amino acid residue not capable of forming a disulfide bond, the mutant ribonuclease inhibitor having a greater resistance to oxidation, the mutant ribonuclease inhibitor retaining its specificity and binding affinity to ribonuclease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-10 are so broad as to encompass any mutant ribonuclease inhibitor having at least one amino acid substitution in at least one of its adjacent cysteine residues to an amino acid residue not capable of forming a disulfide bond, the mutant ribonuclease inhibitor having a greater resistance to oxidation, the mutant ribonuclease inhibitor retaining its specificity and binding affinity to ribonuclease. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of mutant ribonuclease inhibitors broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the mutant human ribonuclease inhibitor wherein said mutation

is a substitution in at least one of its two adjacent cysteine residues to an amino acid residue not capable of forming a disulfide bond, the mutant ribonuclease inhibitor having a greater resistance to oxidation, the mutant ribonuclease inhibitor retaining its specificity and binding affinity to ribonuclease.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any mutant ribonuclease which comprises said cysteine mutations because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting ribonuclease inhibitor activity and oxidative resistance; (B) the general tolerance of ribonuclease to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of amino acid modifications of any ribonuclease inhibitor. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of those mutants having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Chen et al. (Proc. Natl. Acad. Sci. USA 94: 1761-1766, March 1997).

Chen et al. teach the site-specific mutagenesis of human ribonuclease inhibitor (hRI) and how this reveals differences in the structural bases for tight binding of RNase inhibitor to angiogenin and RNase A. Specifically Chen et al. create a C408A mutant of hRI and show that the kinetics of dissociation of this mutant RI with RNase A was similar to that of the wildtype RI

(page 1763, second column). Thus based on the above discussion above under 112 2nd paragraph regarding the possible interpretation of claim 1 Chen et al. anticipates this claim.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on M-F from 7:30 to 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapy Achutamurthy (Murthy), can be reached on (703) 308-3804. The fax number for Official Papers to Technology Center 1600 is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Richard Hutson Ph.D.
12/29/2000

PONNATHAPU ACHUTA...
SUPERVISORY ... EXA...
TECHNOLOGY ...